

Personalized maintenance therapy in advanced non-small cell lung cancer

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Abstract: Maintenance therapy is a treatment strategy that can prolong survival in patients with advanced non-small cell lung cancer (NSCLC). The increased survival achieved with maintenance therapy has led to new treatment options that should be chosen in accordance with the preferences of patients and physicians. Personalized maintenance therapy involves identification of histological subtypes and molecular features of tumors, thereby improving treatment outcomes. Many clinical trials have been conducted to establish new treatment strategies for patients with advanced NSCLC with non-squamous cell histology. The discovery of epidermal growth factor receptor (EGFR) mutations was the most significant innovation for personalized therapy in NSCLC patients. First generation EGFR-tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have significantly contributed to greatly increased survival in specific patients harboring activating EGFR mutations such as exon 19 deletion and L858R point mutation. Based on clinical trials of different maintenance therapy strategies, we identified the regimen is the most promising and highlighted for patients whom should be given specific kinds of therapy now and in future studies.

Keywords: EGFR mutation; non-small cell lung cancer (NSCLC); personalized therapy



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Lung cancer is the leading cause of cancer-related death worldwide (1). Efforts to improve the survival of non-small cell lung cancer (NSCLC) patients are currently focused on the development of innovative personalized treatment options, particularly with molecular targeted therapy or maintenance therapy.

The accepted standard first-line treatment for patients with unselected advanced NSCLC is a platinum-based agent in combination with gemcitabine, vinorelbine, irinotecan, docetaxel, or paclitaxel (2-5). Recent studies demonstrated that cisplatin or carboplatin plus pemetrexed and carboplatin plus paclitaxel plus bevacizumab conferred a survival advantage compared to other regimens in a limited number of NSCLC patients with non-squamous cell histology (6,7). Currently, personalized therapy may contribute to improved survival through identification of specific genotypic anomalies and histologic subtypes in each patient.

Both gefitinib and erlotinib are reversible inhibitors of

the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). Erlotinib led to prolonged survival in a group of previously treated NSCLC patients who were not selected for EGFR mutations, whereas gefitinib did not improve survival in a similar population (8,9). Erlotinib and docetaxel are recommended for previously treated NSCLC patients according to American Society of Clinical Oncology (ASCO) guidelines. In a recent randomized phase III trial (DELTA) in unselected, previously treated NSCLC patients, erlotinib failed to result in better progression-free survival (PFS) than docetaxel (10). However, significantly longer PFS was seen in EGFR-wild type patients treated with docetaxel. Several prospective studies of gefitinib and erlotinib demonstrated significantly increased response rates and marked improvement in PFS compared to standard chemotherapy in selected populations harboring activating EGFR mutations including exon 19 deletion and L858R point mutation (11-14). According to these

results, first-generation EGFR-TKIs are most effective in specific patients with NSCLC who have activating EGFR mutations.

Maintenance therapy is the continued treatment of a tumor that has not progressed after initial induction chemotherapy. Previous studies have demonstrated the utility and safety of switch or continuation maintenance chemotherapy after induction treatment with platinum-based combination chemotherapy (15,16). The AVAiL study (17), FLEX study (18), and ECOG 4599 study (7), large randomized phase III trials of continuation therapy with bevacizumab (AVAiL, ECOG 4599) or cetuximab (FLEX) after first-line chemotherapy, met their primary endpoints with significantly longer overall survival (OS) or PFS. The AVAiL and ECOG 4599 studies enrolled patients with non-squamous cell histology, and the FLEX study selected patients with EGFR positivity by immunohistochemistry. The first-line treatment differed between the control group and the treatment group in these studies. The chemotherapy regimen used for first-line therapy in each trial may influence survival. Therefore, it is difficult to draw conclusions about the benefits of continuation treatment after first-line therapy from these studies. Given this limitation, it is unclear whether bevacizumab and cetuximab, which were continually administered after first-line chemotherapy in these studies, are effective agents for maintenance therapy.

The AVAPERL study was a randomized phase III trial of maintenance bevacizumab with or without pemetrexed administered after first-line induction chemotherapy with cisplatin plus pemetrexed and bevacizumab in advanced NSCLC patients with non-squamous cell histology. In this study, patients treated with maintenance pemetrexed plus bevacizumab had a longer PFS (19). Given the results of the previous large phase III studies as well as AVAPERL, pemetrexed plus bevacizumab may currently be the most highly recommended maintenance regimen in NSCLC patients with non-squamous cell histology. The ECOG 5508 study, which is an ongoing randomized phase III trial, compares maintenance with bevacizumab alone to maintenance with bevacizumab plus pemetrexed or pemetrexed alone after treatment with carboplatin, paclitaxel, and bevacizumab in selected NSCLC patients with non-squamous cell histology (20). The results of this trial will allow confirmation of the most appropriate maintenance therapy.

There are two randomized phase III trials of maintenance therapy that demonstrated longer PFS and OS in selected

patients with advanced NSCLC. The PARAMOUNT study assessed the efficacy of maintenance therapy with pemetrexed after completion of cisplatin plus pemetrexed in patients with advanced non-squamous NSCLC (21,22). The SATURN trial assessed the efficacy of erlotinib as maintenance therapy after completion of first-line platinum-doublet chemotherapy (23). These studies demonstrated longer PFS and OS with maintenance therapy than in a placebo control group. Given these results, the current recommendation is continuation maintenance therapy with pemetrexed for patients with advanced NSCLC with non-squamous cell histology, and switch maintenance therapy with erlotinib for patients with unselected advanced NSCLC. The latter regimen is especially recommended for patients who showed response with stable disease to induction platinum-doublet chemotherapy (24).

Previously, the WJTOG0203 study showed significantly long PFS in Japanese patients with NSCLC who were treated with continuation gefitinib after completion of first-line platinum-doublet chemotherapy (25). However, patients enrolled in this study randomly received either platinum-doublet chemotherapy for up to six cycles or platinum-doublet chemotherapy for three cycles followed by gefitinib. The number of treatment cycles given during first-line chemotherapy was different between the treatment and control groups in this study. Therefore, it is difficult to draw conclusions about the efficacy of gefitinib as switch maintenance therapy in these unselected NSCLC patients. The INFORM trial, which was a phase III study of gefitinib as switch maintenance treatment in patients who completed first-line platinum-based chemotherapy during induction, showed significantly longer PFS in patients with advanced NSCLC (26). This study is the first phase III trial to assess the efficacy of gefitinib as maintenance treatment in Asian patients with advanced NSCLC who achieved disease control with platinum-based induction chemotherapy. This study met its primary endpoint, with significantly increased PFS in patients who received gefitinib, as indicated by histology analysis and biomarker measurement, compared to the placebo group in unselected patients. This study strongly suggests that maintenance therapy with gefitinib conferred considerable survival benefit on specific patients who had activating EGFR mutations, including exon 19 deletion and L858R point mutation, but no PFS benefit on patients who had wild-type EGFR.

While both gefitinib and erlotinib have potential for maintenance therapy in EGFR-mutated NSCLC patients, the efficacy of each agent was determined by subset

analysis of randomized phase III studies including the INFORM and SATURN trials. These studies demonstrated the important fact that first-generation EGFR-TKIs used as switch maintenance therapy may produce a significant improvement in PFS for a limited group of NSCLC patients who harbor EGFR mutations and who achieve disease control after first-line platinum-doublet chemotherapy when compared to the placebo group. However, EGFR-TKIs need to undergo more thorough assessment as switch maintenance therapy before they are fully accepted as a standard treatment. First, studies must analyze whether these switch maintenance regimens would show increased PFS and/or OS benefits compared to a strategy in which treatment would not begin until after the disease is progressive (watch and wait) in NSCLC patients harboring EGFR mutations. Second, the efficacy of first-generation EGFR-TKIs as first-line therapy should be examined to determine whether their use in maintenance therapy is really the best way to increase survival. Finally, studies must determine whether gefitinib or erlotinib is the most promising agent for switch maintenance therapy.

The most recommended first-line chemotherapy regimen as induction treatment in patients with advanced NSCLC is unclear. Large prospective phase III trials comparing first-line chemotherapy regimens as induction treatments are lacking. According to previous studies, platinum-based chemotherapy including pemetrexed is considered the best treatment chemotherapy regimen in patients with non-squamous cell NSCLC. The POINTBREAK study (27), which was a randomized phase III study, was designed to assess whether pemetrexed plus carboplatin plus bevacizumab followed by pemetrexed plus bevacizumab was superior to paclitaxel plus carboplatin plus bevacizumab followed by bevacizumab for advanced non-squamous cell NSCLC. However, no significant difference was observed in terms of the primary endpoint of OS in either group, and this study failed to show a positive outcome. Additionally, Zinner *et al.* reported at the 2013 ASCO annual meeting that the PRONOUNCE study, which was a randomized phase III trial of carboplatin plus pemetrexed (plus maintenance pemetrexed), found no significant difference in PFS or OS compared to carboplatin plus paclitaxel plus bevacizumab (plus maintenance bevacizumab) according to subset analysis (28). Platinum-based combination chemotherapy with pemetrexed or paclitaxel (with bevacizumab) is recommended as induction chemotherapy for non-squamous cell NSCLC.

In summary, platinum-based combination chemotherapy

with pemetrexed or carboplatin plus paclitaxel plus bevacizumab is recommended as the induction chemotherapy regimen in patients with non-squamous cell NSCLC. Pemetrexed plus bevacizumab is potentially more effective as a continuation or switch maintenance regimen than pemetrexed in this same population. First-generation EGFR-TKIs including gefitinib and erlotinib as switch maintenance therapies may prominently prolong PFS in patients harboring activating EGFR mutations. However, several prospective studies are needed to assess the efficacy of those molecular agents as maintenance therapy in selected patients with activating EGFR mutations. Since no trials have compared maintenance therapy with cytotoxic agents versus targeted agents in EGFR-mutated patients, data about the advantage of these maintenance therapies are inconclusive. Recently, the FASTACT-2 study (29), which was randomized phase III trial of chemotherapy plus erlotinib followed by erlotinib, demonstrated longer PFS and OS in unselected NSCLC patients. The difference was particularly large in patients harboring activating EGFR mutations. Chemotherapy plus EGFR-TKIs followed by EGFR-TKIs may come to be a new strategy for EGFR-mutated NSCLC. In the future, specific clinical studies are needed to establish new strategies for maintenance therapy in EGFR-mutated patients and in patients with squamous cell histology without activating EGFR mutations.

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References

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300.
2. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317-23.
3. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007;99:847-57.
4. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of

- the published literature. *J Clin Oncol* 2005;23:2926-36.
5. Rajeswaran A, Trojan A, Burnand B, et al. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. *Lung Cancer* 2008;59:1-11.
 6. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-51.
 7. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542-50.
 8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.
 9. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527-37.
 10. Okano Y, Ando M, Asami K, et al. Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol* 2013;31:abstr 8006.
 11. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121-8.
 12. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
 13. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-46.
 14. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-42.
 15. Bylicki O, Ferlay C, Chouaid C, et al. Efficacy of pemetrexed as second-line therapy in advanced NSCLC after either treatment-free interval or maintenance therapy with gemcitabine or erlotinib in IFCT-GFPC 05-02 phase III study. *J Thorac Oncol* 2013;8:906-14.
 16. Belani CP, Brodowicz T, Ciuleanu T, et al. Maintenance pemetrexed (Pem) plus best supportive care (BSC) versus placebo (Plac) plus BSC: A randomized phase III study in advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2009;27;abstr CRA8000.
 17. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol* 2009;27:1227-34.
 18. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009;373:1525-31.
 19. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol* 2013;31:3004-11.
 20. Dahlberg SE, Ramalingam SS, Belani CP, et al. A randomized phase III study of maintenance therapy with bevacizumab (B), pemetrexed (Pm), or a combination of bevacizumab and pemetrexed (BPm) following carboplatin, paclitaxel and bevacizumab (PCB) for advanced nonsquamous NSCLC: ECOG trial 5508 (NCT01107626). *J Clin Oncol* 2011;29;abstr TPS218.
 21. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (Paramount): a double-blind, phase 3, random. *Lancet Oncol* 2012;13:247-55.
 22. Paz-Ares L, De Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed(pem)plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung

- cancer (NSCLC). *J Clin Oncol* 2012;30:abstr LBA7507.
23. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521-9.
 24. Coudert B, Ciuleanu T, Park K, et al. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. *Ann Oncol* 2012;23:388-94.
 25. Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). *J Clin Oncol* 2010;28:753-60.
 26. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet Oncol* 2012;13:466-75.
 27. Patel J, Socinski MA, Garon EB, et al. A Randomized, Open-label, Phase 3, Superiority Study Of Pemetrexed (Pem)+Carboplatin (Cb)+Bevacizumab (B) Followed By Maintenance Pem+B Versus Paclitaxel (Pac)+Cb+B Followed By Maintenance B In Patients (pts) With Stage IIIB Or IV Non-squamous Non-small Cell Lung Cancer (NS-NSCLC). Presented at: 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology. 2012; Chicago, IL. Abstract LBPL1.
 28. Zinner R, Ross HJ, Weaver R, et al. Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab (PCB) followed by maintenance bevacizumab in patients with advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). *J Clin Oncol* 2013;31:abstr LBA8003.
 29. Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. *Lancet Oncol* 2013;14:777-86.

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